UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

June 2, 2000

OFFICE OF
THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

Note to the Reader:

The attached draft report is a draft report of the Science Advisory Board (SAB). The draft is still undergoing final internal SAB review, however, in its present form, it represents the consensus position of the panel involved in the review. Once approved as final, the report will be transmitted to the EPA Administrator and will become available to the interested public as a final report.

This draft has been released for general information to members of the interested public and to EPA staff. This is consistent with the SAB policy of releasing draft materials only when the Committee involved is comfortable that the document is sufficiently complete to provide useful information to the reader. The reader should remember that this is an unapproved working draft and that the document should not be used to represent official EPA or SAB views or advice. Draft documents at this stage of the process often undergo significant revisions before the final version is approved and published.

The SAB is not soliciting comments on the advice contained herein. However, as a courtesy to the EPA Program Office which is the subject of the SAB review, we have asked them to respond to the issues listed below. Consistent with SAB policy on this matter, the SAB is not obligated to address any responses which it receives.

1. Has the Committee adequately responded to the questions posed in the Charge?
2. Are any statements or responses made in the draft unclear?
3. Are there any technical errors?

For further information or to respond to the questions above, please contact:

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CANCER RISK ASSESSMENT GUIDELINES REVIEW SUBCOMMITTEE

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APPLICATION OF THE CANCER RISK ASSESSMENT GUIDELINES TO CHILDREN

May 19, 2000

EXECUTIVE COMMITTEE REVIEW DRAFT

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June XX, 2000

EPA-SAB-EC-00-00X

Honorable Carol Browner
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: Review of the Draft Cancer Risk Assessment Guidelines' Application to Children

Dear Ms. Browner:

The Cancer Risk Assessment Guidelines Review Subcommittee (CRAGRS) of the US EPA Science Advisory Board (SAB) met on July 27 and 28, 1999, in Arlington Virginia.. The purpose of the meeting was to provide advice and comment to the EPA on issues related to applying the provisions of EPA's proposed revised Cancer Risk Assessment Guidelines (GLs) to children.

In April 1996, EPA proposed revisions to the 1986 Guidelines (61 *Federal Register* 17960-18011). In 1997, the SAB reviewed the Proposed Guidelines (EPA-SAB-EHC-97-010) and generally commended the Agency for its efforts to incorporate new scientific information. In early 1999, the SAB reviewed selected sections of the 1996 Proposed Guidelines that were revised to address SAB and public recommendations dealing with hazard descriptors, the use of mode of action information, dose-response analysis, and the approach to the use of margin of exposure analysis. The SAB (EPA-SAB-EC-99-014) recommended that the Agency move ahead and consolidate the progress made to date.

One outstanding issue from the earlier SAB reviews is the recommendation to expand the discussion in the Guidelines regarding special subpopulations, particularly children. The Agency has now requested the SAB's advice and comment on further revisions to the Guidelines intended to address children's risk.

The Charge for the current review focused on the adequacy of the general guidance provided in various sections of the revised GLs (i.e., the supplementary information section of the introduction, and the hazard assessment, dose-response assessment, exposure assessment and risk characterization chapters) on how to incorporate relevant data into the evaluation of carcinogenic risk to special subpopulations, in particular children. Specific questions posed in the Charge include:

a) The soundness of default science policy positions as they relate to assessing children's risk in the absence of data. In particular:

   1) Given the current state of knowledge, the draft guidelines assume that the upper bound of the linear default procedure adequately accounts for variability unless there is case-specific information for a given agent that indicates a particularly sensitive subpopulation, for which case, an additional factor may be considered. Does the SAB agree that this default position reflects the current state of the information and represents an appropriate public health protective approach?

   2) The Mode of Action (MOA) Framework provides for analysis of all data as to relevance to humans including subpopulations of concern (e.g., children). A scientific rationale is to be provided covering the possible similarities and differences of the MOA among the human population. This judgment could be made from inferences without actual data on these subpopulations. Please comment on this position given the current knowledge about mode of carcinogenic action in the human population exposed to environmental agents.

b) Does the SAB agree with the default position recommending the addition of a 10-fold factor to account for the variability in cancer responsiveness in the general population (unless case-specific information indicates that a greater factor is appropriate) when a a margin of exposure approach is used?

c) Are the default approaches for converting a point of departure derived for adults into a point of departure to apply to children reasonable, in light of what is known about doses to children, the information that will typically be available to the risk assessor, and the Agency's policy of erring on the side of children's health when information is not available?

d) Is the approach for adjusting slope factors in lifetime and partial lifetime exposure scenarios (to reflect data on early-life sensitivity) appropriate?

At the request of the Office of Research and Development, the Subcommittee also evaluated the responsiveness of the draft guidelines to the questions posed by the EPA Children's Health Protection Advisory Committee in its May 12, 1999 letter to Administrator Browner. Although the Committee judged the responses for the most part to be adequate, some were rather perfunctory and incomplete. Several suggestions for improvement are detailed in Section 3.6 of the enclosed report.

Addressing the broad issues of applying the GLs, the Subcommittee urges EPA to issue the Guidelines promptly (with attention to the suggestions in this report) and then undertake a program of research and risk assessment improvement that will enable it to address the childhood susceptibility issue more completely in future revisions of the Guidelines.

The following discussion summarizes the Subcommittee's findings (often expressed as a range of views rather than a consensus) on the five primary issues posed by the Charge.

The Subcommittee examined the use of a linear default approach and whether use of this default position represents an appropriate public health protective approach for children. Most of the Subcommittee agreed that the linear default approach (using the "upper bound" estimate) was sufficiently conservative. Several Subcommittee Members believed that the current procedure could mis-predict risk and did not provide assurance of public health protection.

The Subcommittee believes that the Mode of Action Framework for analysis of data proposed by the Agency, should be relevant for most subpopulations of concern. It is important, however, to consider a special evaluation which would determine whether all assumptions based on an adult "mode of action" would apply across the entire time-span of childhood., and would consider different exposure scenarios.

The Subcommittee was unable to reach a consensus on the default use of a 10-fold adjustment factor (when application of the Framework for assessing mode of action data establishes that linearity is not the most reasonable working judgment and that there is sufficient evidence to support a nonlinear mode of action). The Members did agree with the supposition that, even after adjusting for differences in exposure, the population response threshold for children could be lower than for adults for some carcinogens acting through a non-linear mode of action. Various Members had differing perceptions about how often increased sensitivity of children actually occurs and whether EPA should routinely apply a separate factor to increase children's protection. There was consensus that if EPA were to use such a factor, it should be dependent on the state of the database and not a single default number. In general, the Subcommittee was supportive of EPA's intent to evaluate the acceptability of an MOE on a case-by-case basis, supported by a narrative.

Some Members of the Subcommittee agreed with EPA's default assumption that the mode of action should not be considered operative in children and a linear dose-response relationship be used unless a biologically cogent rationale is developed or agent specific data is available. Other Members found the EPA's default assumption and policy inconsistent with the EPA's general conclusion that the mode of action is similar between children and adults (GL p. xii-xiii). A more consistent policy decision would be to apply a margin of exposure approach when a non-linear mode of action has been established in adults. EPA could require an additional uncertainty factor if there are data to suggest that children are greater than 10 times more susceptible than adults.

The Subcommittee felt that the Agency's default approaches for converting adult doses into doses applicable to children must assure that the defaults take into account, within the capability of the extant knowledge base, all the changing biological factors of childhood development. However, if the Agency continues under the current framework, it should be internally consistent in its approach to adjusting doses for the various routes of exposure. More

specifically, the Subcommittee noted that EPA's default approach for converting an equivalent dose for adults to an equivalent dose for children is unclear and needs better definition.

In general, the Subcommittee found that the approaches to adjusting slope factors for lifetime and partial lifetime exposure scenarios to reflect data on early-life sensitivity were appropriate, but some Members felt the procedure might be improved. These Members encouraged the Agency to evaluate mathematical modeling approaches to account for age dependencies. The Members also felt that changes should be made to improve the clarity of the presentation in the Guidelines document, especially in the examples provided in the Guidelines' Appendix F.

The Subcommittee recognizes the care and effort that the EPA has applied in developing these draft Guidelines. The Subcommittee commends the EPA on their diligence. The EPA and the Subcommittee appreciates the need to have the Guidelines be health protective, particularly to children, and scientifically valid, while making sure the document is a living document that allows the applications of new knowledge, thought, and technology.

We appreciate the opportunity to review these issues, and look forward to your response.

Sincerely,

Dr. Morton Lippmann, Interim Chair
Science Advisory Board

Dr. Mark Utell, Co-Chair
Cancer Guidelines Risk Assessment
Review Subcommittee
Science Advisory Board

NOTICE

ABSTRACT

TO BE SUPPLIED

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1. EXECUTIVE SUMMARY

The Cancer Risk Assessment Guidelines Review Subcommittee (CRAGRS) of the US EPA Science Advisory Board (SAB) met on July 27 and 28, 1999, in Arlington Virginia.. The purpose of the meeting was to provide advice and comment to the EPA on issues related to applying the provisions of EPA's proposed revised Cancer Risk Assessment Guidelines (GLs) to children. The Agency sought advice from the SAB on a range of issues, especially focusing on the adequacy of the GLs when dealing with assessing risks to children. (the complete Charge is provided in section 2.2 of this report).

Addressing the broad issues of applying the GLs, the Subcommittee urges EPA to issue the Guidelines promptly (with attention to the suggestions in this report) and then undertake a program of research and risk assessment improvement that will enable it to address the childhood susceptibility issue more completely in future revisions of the Guidelines.

The following discussion summarizes the Subcommittee's findings (often expressed as a range of views rather than a consensus) on the five primary issues posed by the Charge.[1]
The Subcommittee examined the use of a linear default approach and whether use of this default position represents an appropriate public health protective approach for children. Most of the Subcommittee agreed that the linear default approach (using the "upper bound" estimate) was sufficiently conservative. Several Subcommittee Members believed that the current procedure could mis-predict risk and did not provide assurance of public health protection.

The Subcommittee believes that the Mode of Action Framework for analysis of data proposed by the Agency, should be relevant for most subpopulations of concern. It is important, however, to consider a special evaluation which would determine whether all assumptions based on an adult "mode of action" would apply across the entire time-span of childhood., and would consider different exposure scenarios.

[1] The Subcommittee also evaluated the responsiveness of the draft guidelines to the questions posed by the EPA Children's Health Protection Advisory Committee in its May 12, 1999 letter to Administrator Browner. Although the Committee judged the responses for the most part to be adequate, some were rather perfunctory and incomplete. Several suggestions for improvement are detailed in Section 3.6.

The Subcommittee was unable to reach a consensus on the default use of a 10-fold adjustment factor (when application of the Framework for assessing mode of action data establishes that linearity is not the most reasonable working judgment and that there is sufficient evidence to support a nonlinear mode of action). The Members did agree with the supposition that, even after adjusting for differences in exposure, the population response threshold for children could be lower than for adults for some carcinogens acting through a non-linear mode of action. Various Members had differing perceptions about how often increased sensitivity of children actually occurs and whether EPA should routinely apply a separate factor to increase children's protection. There was consensus that if EPA were to use such a factor, it should be dependent on the state of the database and not a single default number. In general, the Subcommittee was supportive of EPA's intent to evaluate the acceptability of an MOE on a case-by-case basis, supported by a narrative.

Some Members of the Subcommittee agreed with EPA's default assumption that the mode of action should not be considered operative in children and a linear dose-response relationship be used unless a biologically cogent rationale is developed or agent specific data is available. Other Members found the EPA's default assumption and policy inconsistent with the EPA's general conclusion that the mode of action is similar between children and adults (GL p. xii-xiii). A more consistent policy decision would be to apply a margin of exposure approach when a non-linear mode of action has been established in adults. EPA could require an additional uncertainty factor if there are data to suggest that children are greater than 10 times more susceptible than adults.

The Subcommittee felt that the Agency's default approaches for converting adult doses into doses applicable to children must assure that the defaults take into account, within the capability of the extant knowledge base, all the changing biological factors of childhood development. However, if the Agency continues under the current framework, it should be internally consistent in its approach to adjusting doses for the various routes of exposure. More specifically, the Subcommittee noted that EPA's default approach for converting an equivalent dose for adults to an equivalent dose for children is unclear and needs better definition.

In general, the Subcommittee found that the approaches to adjusting slope factors for lifetime and partial lifetime exposure scenarios to reflect data on early-life sensitivity were appropriate, but some Members felt the procedure might be improved. These Members encouraged the Agency to evaluate mathematical modeling approaches to account for age dependencies. The Members also felt that changes should be made to improve the clarity of the presentation in the Guidelines document, especially in the examples provided in the Guidelines' Appendix F.

The Subcommittee recognizes the care and effort that the EPA has applied in developing these draft Guidelines. The Subcommittee commends the EPA on their diligence. The EPA and the Subcommittee appreciates the need to have the Guidelines be health protective, particularly to children, and scientifically valid, while making sure the document is a living document that allows the applications of new knowledge, thought, and technology.

2 INTRODUCTION

2.1 Background

In September 1986, EPA published *Guidelines for Carcinogen Risk Assessment* (51 *Federal Register* 33992-34003). Since that time, significant gains have been made in understanding the carcinogenic process while the Agency's experience with the 1986 Guidelines has revealed several limitations in their approach to cancer risk assessment. In April 1996, EPA proposed revisions to the 1986 Guidelines (61 *Federal Register* 17960-18011). These revisions are the result of a number of EPA-sponsored meetings, e.g., a 1994 peer review workshop (*Report on the Workshop on Cancer Risk Assessment Issues*, EPA/630/R-94/005a), recommendations contained in the National Academy of Sciences (NAS) 1994 report *Science and Judgment in Risk Assessment,* and extensive EPA and federal reviews.

Standard toxicological testing will rarely provide information that will allow a mode of action determination. Consequently, the default procedures virtually always apply. These are the data that the Agency can reasonably request for the registration of a particular product through authorities like FIFRA and TSCA. These data are used to make some preliminary assessments and if there appears to be an acceptable margin of safety, the product can be manufactured and/or used.

These methods are not appropriate for making refined risk assessments, but they serve us well in limiting the introduction of unsafe products into commerce.

In some much more limited circumstances there are a variety of reasons why data more appropriate for estimating risks are gathered. These data may be epidemiological when exposures do occur or they may be toxicological data gathered in humans or experimental animals under controlled conditions. These data include better estimates of the exposure variables, including differences that might be encountered by age. They may include a better understanding of how a chemical produces its effects, ranging from information on the metabolism of the chemical, how that affects the toxicity, and how these variables change with age. Finally, some work focuses on some of the mechanisms that are responsible the toxic response. Each of these data types improves our ability to assess risk. More important they put us in a much better position of how those risks may vary in a population. The new Guidelines open up the possibility of utilizing these data.

It is extremely important that this new direction not undermine the time honored procedures that have been used for over a half a century for the purpose of protecting the public health. These tests have been developed and selected with the notion of assessing as broadly and inexpensively as possible the probability that a chemical or a product can do harm to human health under conditions of use. Large uncertainty factors are usually applied to no-effect-levels or an LED_{10} to insure an adequate margin of safety. To be clear, we include 2-year cancer bioassays, 2-generation reproduction studies, and teratology studies in these tests. As expensive as some of these efforts are, it will be rare that mode of action information will be derived on chemicals tested in these studies.

The investment in understanding mode of action of a chemical once this basic information is obtained, will generally exceed the basic investment in routine tests described by an order of magnitude. For this reason alone, research of this type will only be done where there is some recognized societal value in the product/chemical and there are not obvious alternatives.

The intent of the revised Guidelines is to take into account the available knowledge about the carcinogenic process and to provide flexibility for the future in assessing data, recognizing that the Guidelines cannot always anticipate future research findings. Compared to the 1986 Guidelines, the revised Guidelines emphasize a more complete evaluation of all relevant information and provide more guidance on the use of information on the way an agent produces cancer (mode of action). The emphasis on mode of action is intended to help reduce the uncertainties associated with assessing and characterizing human cancer risk and to help identify whether there is special concern for particular subpopulations, e.g., children. The revised Guidelines are structured on an analytical framework that recognizes a variety of conditions under which the cancer hazard may be expressed (e.g., route or magnitude of exposure to the agent). The revised Guidelines retain the Agency's traditional use of a linear low dose extrapolation as a default procedure to quantify possible human cancer risks. However, the Guidelines recognize that different modes of action for carcinogenicity (e.g., direct action with DNA, hormonal or other growth-signaling processes) are being elucidated as the scientific understanding of the carcinogenic processes advances. The Agency will increasingly need to assess mechanistic studies that have implications for hazard, dose-response, and risk characterization.

In February 1997, the SAB reviewed the Proposed Guidelines (EPA-SAB-EHC-97-010) and generally commended the Agency for its efforts to incorporate new scientific information and for being responsive to recommendations from authoritative groups, e.g., the NAS and the

Presidential/Congressional Commission on Risk Assessment and Risk Management (GPO #55-000-00568-1, 1997). On January 20-21, 1999 at the request of the Agency, the SAB reviewed selected sections of the 1996 Proposed Guidelines that were revised to address SAB and public recommendations dealing with hazard descriptors, the use of mode of action information, dose-response analysis, and the approach to the use of margin of exposure analysis. The report (EPA-SAB-EC-99-014) from the January review recommends that the Agency move ahead and consolidate the progress made to date. One outstanding issue from the earlier SAB reviews is the recommendation to expand the discussion in the Guidelines regarding special subpopulations, particularly children. The Agency is now requesting the SAB's advice and comment on certain revised sections of the Guidelines that address children's risk. The review document[2] contains highlighted text throughout the document that is intended to raise the awareness of risk assessors to the issue of children as a special subpopulation either because it is possible that children may be more highly exposed and/or more uniquely susceptible than the adult population. Where appropriate, guidance is provided and risk assessors are directed to Agency methods and data sources that are useful in conducting assessments for children. The Agency envisions that the revised cancer guidelines will be used in concert with the Agency's existing risk assessment guidelines addressing mutagenicity, developmental toxicity, reproductive toxicity, neurotoxicity, and exposure. All of these guidelines will be consulted when conducting risk assessments to ensure that information from studies on carcinogenesis and other health effects is considered together in an overall characterization of risks to children. From time to time, EPA revises its risk assessment guidelines to reflect advances in the science or methodologies and also produces supplementary guidance that expands more fully on issues touched upon in the guidelines, e.g., guidance on the assessment of renal tumors in male rats (EPA, 1991), guidance on the assessment of thyroid follicular cell tumors (EPA 1998), and guidance on conducting probabilistic risk assessments (EPA, 1998). EPA intends to continue with this practice and supplement the revised cancer guidelines through peer consultation workshops and peer reviewed guidance. Areas that will receive particular emphasis include: how to better inform and improve the assessment of children's risk, inter-individual

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[2]The current document constitutes work in progress. It incorporates some changes to the January 1999 review draft based on discussions at the January meeting and the draft letter from the Science Advisory Board (SAB), dated May 27, 1999. The Agency is continuing to address the SAB recommendations. However, for the purpose of providing a context for a discussion of the guidance on assessing children's risk, the Agency has provided the most current version of the draft guidelines.

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variability in toxicokinetic behavior of the chemical and the toxicodynamics of the response it elicits , and methodologies for margin of exposure analysis and other dose-response approaches.

The Agency sought the Science Advisory Board's review of the revisions to the draft Guidelines for Carcinogenicity as to the adequacy of the general guidance provided in various sections (i.e., the supplementary information section of the introduction, and the hazard assessment, dose-response assessment, exposure assessment and risk characterization chapters) on how to incorporate relevant data into the evaluation of carcinogenic risk to special subpopulations, in particular children. The Guidelines refer to additional guidance in other documents that should be consulted when assessing risk to children.

2.2 Charge

a) The Guidelines contain discussion of a set of major default assumptions adopted in these Guidelines. The Agency seeks the Science Advisory Board's review of the soundness of these default science policy positions as they relate to assessing children's risk in the absence of data. In particular:

1) A linear default approach is used when the mode of action information is supportive of linearity or, alternatively, when the information is insufficient to support a nonlinear mode of action. The linear default approach is generally thought to produce an upper bound on potential risk at low doses, e.g., a 1/100,000 to 1/1,000,000 risk; the straight line approach described in the draft guidelines gives numerical results about the same as a linearized multistage procedure. Given the current state of knowledge, the draft guidelines assume that the upper bound of the linear default procedure adequately accounts for variability unless there is case-specific information for a given agent that indicates a particularly sensitive subpopulation, for which case, an additional factor may be considered. Does the SAB agree that this default position reflects the current state of the information and represents an appropriate public health protective approach?

2) The Mode of Action (MOA) Framework provides for analysis of all data as to relevance to humans including subpopulations of concern (e.g., children). A scientific rationale is to be provided covering the possible similarities and differences of the MOA among the human population. This judgment could be made from inferences without actual data on these subpopulations. Please comment on this position given the current knowledge about mode of carcinogenic action in the human population exposed to environmental agents.

b) When application of the Framework for assessing mode of action data establishes that linearity is not the most reasonable working judgment and that there is sufficient evidence to support a nonlinear mode of action, a margin of exposure approach is taken. In carrying out this analysis, the 1996 Proposed Guidelines recommend a factor of 10-fold to account for the variability in cancer responsiveness in the general population, unless case-specific information indicates that a greater factor is appropriate. Does the SAB agree with this default position?

c) The Guidelines describe the following default approaches for converting a point of departure derived for adults into a point of departure to apply to children: for oral exposure, use the adult LED_{10} that was based on the 3/4 power of relative body weight; for inhalation exposure, convert an LEC_{10} to reflect a child's inhalation rate and body weight. Are these default approaches reasonable, in light of what is known about doses to children, the information that will typically be available to the risk assessor, and the Agency's policy of erring on the side of children's health when information is not available?

d) The Guidelines provide an example of how slope factors can be adjusted in lifetime and partial lifetime exposure scenarios to reflect data on early-life sensitivity. Is this approach appropriate?

e) In a letter to Administrator Browner, dated May 12, 1999, the EPA Children’s Health Protection Advisory Committee (CHPAC) suggested a series of questions that should be considered by the Science Advisory Board in reviewing how the draft revisions to the Guidelines provide bases for future Agency decisions that fully consider the risk of prenatal and childhood exposure and cancer. The Agency has prepared responses to the questions posed in the CHPAC letter.[3] The Science Advisory Board is asked to review and comment on the Agency's responses. The questions are:

1. When scientific data suggest a mode of action, what data should be required, if any, to establish its relevance to humans? (6)

2. Are modes of action for chemicals different for children than for adults? (2)

3. What constitutes sufficient mode of action data to depart from a linear default dose response that is adequate for children and for adults? What policy should be implemented in the absence of mode of action data to assure protection of children? What policy should be followed if there are sufficient data to establish a mode of action in an adult, but not for a fetus or child? (1)

4. What examples of unique childhood cancers or cancers in adult life following childhood exposure have been considered in developing the guidelines? (9a)

5. What factors should be reviewed to determine the latent risks from exposures at different developmental stages (preconception, in utero, childhood, adolescence)? (3)

6. How do the guidelines account for the timing of exposure, especially acute exposures at sensitive developmental stages? (4)

7. How should exposure assessments for special populations be addressed? Should examples be given? (7)

8. Are new models for acute or combined acute/chronic exposure needed? (9b)

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[3] The CHPAC letter posed nine questions. In responding, however, the EPA reorganized the questions, and divided one into two parts, resulting in the ten questions listed above. The original number is shown in parentheses at the end of each question.

9. What research should EPA sponsor to improve its ability to evaluate the susceptibility of high-risk populations, including children? (8)

10. How do the proposed guidelines take into account the sequencing of sensitizing and subsequent potentiating events in the manifestation of cancers both in childhood and in later adolescent or adult life (e.g., how might an exposure to a medical intervention such as radiation, chemotherapy, vaccine or virus affect an individual's sensitivity to later environmental or developmental stress factors, such as onset of puberty or exposure to a chemical agent)? (5)

3. DETAILED RESPONSE

3.1 Soundness of the Default Science Policy Positions

The draft Guidelines assume that the upper bound of the linear default procedure adequately accounts for human variability unless there is case-specific information for a given agent that indicates a particularly sensitive subpopulation. EPA asked if the SAB agreed that this default position is appropriate.

Despite a number of important caveats that are subsequently examined, most of the Subcommittee endorsed EPA's position that the existing linear default process of estimating human doses associated with low levels of lifetime cancer risk (one per million to one in 10,000) generally provides adequate protection for sensitive subpopulations. That process employs low-dose linear extrapolation, uses the most sensitive tumor site from animal bioassays (including benign tumors and often based on tumor types with high spontaneous background incidence), and uses cross-species dose scaling on the basis of body weight to the 3/4 power when pharmacokinetic data are lacking. These Members believe that the default may not account for all the uncertainty in the risk estimate. In any particular instance, these Members felt that children may be more or less susceptible than adults, but the default cancer risk estimation process proposed usually should provide adequate protection in those cases in which children are more susceptible than adults. However, data should always be sought to assure the adequacy of the default to protect children.

Subcommittee Members raised a number of concerns about the linear default and the issue of human variability. The Subcommittee agreed that the question posed in this element of the Charge was not restricted to those aspects of statistical variability encompassed by the "upper bound of the linear default procedure," but rather addressed the issue of human variability in the context of the entire extrapolation process, including high-to-low dose and interspecies extrapolations. In performing the statistical analysis to estimate the slope term in the linear default procedure from bioassay data, it is assumed that each animal in a given dose group faces exactly the same, binomial probability of developing cancer. Under the modeling assumptions made, the reason why one animal develops cancer and another does not is is attributed to the stochastic nature of the process, not to heterogeneity. Because the animal strains used in the bioassay are far more homogeneous genetically than the human population, any given animal study provides little information on possible human heterogeneity. Thus, heterogeneity is not explicitly addressed by the procedure when applied to animal data for a single endpoint. However, selection of the most sensitive tissue site across species, strains, and sexes does represent heterogeneity among animals. When applied to epidemiological data, depending on the analysis performed, heterogeneity can be captured for the group being analyzed (usually an adult, white male occupational cohort); adjustments to the cancer potency are not typically made to account for differences between occupational groups and segments of the general population. Although the linearized procedure does not explicitly take into account heterogeneity, some Members of the Subcommittee believed that, overall, the procedure was conservative.

The Subcommittee raised several other important concerns that will require ongoing evaluations. It emphasizes that an estimate of cancer potency of a chemical based on a single strain (usually inbred) of animals may not provide a representative estimate for that rodent species, let alone for humans. It is suggested that the carcinogen risk assessment guidelines should encourage the calculation of potencies (including confidence bounds) for other tissue sites demonstrating evidence of carcinogenicity in both sexes of all strains/species tested in order to study extra-experimental variation of potency estimates. An understanding of the extra-experimental variation in cancer potency would consider composite potency estimates for experiments where neoplasia is observed at multiple sites.

. Biases toward over-prediction in the default procedure are often cited to justify decisions not to address certain factors in the risk assessment. However, several strong biases toward under-prediction in the general default procedure can also be listed. These include certain assumptions typically made in default assessments which can not be generally supported by fact. There faulty assumptions include the following: that the sequential and simultaneous effects of other exposures, in the background, have no effect ; that transplacental and neonatal exposures do not carry significant risks; that averaged exposure is an appropriate surrogate for large intermittent high exposures; that the effect of age at exposure is unimportant (but may actually affect outcome by an order of magnitude (Murdoch and Krewski, 1986)); that risks derived from occupational studies may be applied to all segments and ages in the population; that pharmacokinetics do not vary significantly with age and sex; and that people are genetically homogeneous.

Several other Members took exception with the comments above Improvements can be made to the standard default approach. Age can be taken into account in the exposure assessment, and even the slope factors can be stratified by age within EPA's proposed guidelines. The slope factors are not necessarily derived from an occupational study serving as the basis for the analysis. In principle, pharmacokinetics could be varied with age and sex. This should be further explored. It is noted, however, that the current draft guidelines require chemical specific carcinogenicity data to take into account differences in potency for different subpopulations and at different life stages. Such specific information is available for few chemicals. Some Members felt greater flexibility was needed in the guidelines to account for age at exposure and heterogeneity in the absence of chemical specific data, as scientific understanding and methodology evolve

Some Members believed that the current default approach in EPA's risk assessment procedure does not assume that people are genetically homogeneous. It doesn't stratify the assessment by genotype simply because stratified risk information is so rare. Risk assessment always ignores some of the variation in the population at risk in order to obtain a reasonably stable estimate of overall population risk. Although risk assessors may indeed use the term "individual risk," there is really no such thing. At the individual level, the person either will or will not get cancer as a result of the exposure. Assessors don't know which answer is true, so they consider the person to be part of some homogeneous group. How much to stratify the total population is a matter of judgment informed by the amount and quality of information at the various levels of stratification. and the known effect(s) of polymorphisms on carcinogenesis and eventual cancers.

Some Members noted the large and growing body of scientific information on genetic polymorphisms and other risk factors indicating differing risks for differing groups in the population. Ultimately this will translate on the individual level to individuals having differing risks or probabilities of developing cancer when exposed to the same level of substance. The likelihood formulation used to estimate cancer potency from animal data assumes that each individual is subject to the same risk and that is matter of chance which animal develops cancer. Thus the homogeneity assumption is embedded in the typical default analysis.

When the influence of genetic polymorphisms and age- or sex-related differences in risk become better understood, EPA will have to decide whether and to what extent risk management decisions will have to change. The Agency would be well advised to begin thinking through this issue now and to prepare position papers that can be tested with the appropriate interested parties. The Subcommittee did not reach consensus on whether EPA should introduce additional safety or uncertainty factors into its risk assessments in anticipation of such changes.

Other factors in the analysis that can produce biases toward under prediction in the use of animal data are the assumption of site concordance in assessments utilizing pharmacokinetic analyses, the failure to address intercurrent mortality , saturable pharmacokinetics of the activation pathway in the bioassay, lack of early in life exposure and cessation of study at two years (see e.g., diethylnitrosamine [Peto *et al*., 1984]). It is unknown how, overall, the biases toward under and over prediction balance one another. Consequently, some Subcommittee members found that because human variability is likely to be the rule rather than the exception, it should be explicitly addressed in risk assessments, even those for which particularly sensitive subpopulations are not explicitly identified. The sensitive populations should include at least the following: children, pregnant females, and subjects with disease states such as asthma, polymorphisms, and concurrent exposure to other environmental chemicals that may increase or decrease the likelihood of cancer.

3.2 Mode of Carcinogenic Action in the Human Population

The Mode of Action (MOA) Framework in the proposed Guidelines provides for analysis of all data as to relevance to humans, including subpopulations of concern (e.g., children). A scientific rationale is to be provided covering the possible similarities and differences of the MOA between animals and humans and among the human population, including subpopulations that my have increased susceptibility such as children. EPA asked the Subcommittee for their opinions as to whether this judgment could be made from inferences without actual data on these subpopulations, given the current knowledge about mode of carcinogenic action in the human population exposed to environmental agents.

The Mode of Action Framework for analysis of data should be relevant for most subpopulations of concern. However, in the case of children, and other subpopulations that may have increased risk, it would be important to consider a special evaluation which would determine whether all assumptions based on ”the typical” adult "mode of action" would apply across the entire time-span in children, and other factors in other subpopulations.That children need special review has been recognized in major legislative and administrative initiatives (FQPA, 19XX; EPA Children's Health Initiative, 19XX). Children constitute a sizeable proportion of the population and in assessing lifetime cancer risks it is noted that all adults must first pass through infancy and childhood. Children may be at higher risk, and disease states that irreversibly alter function will naturally have a greater impact on the public health of a population if the disease state begins in a child as compared to an adult **(will provide**

reference for this statement). The EPA has elected to define childhood as the period from preconception through fetal life and into sexual maturation/adulthood.. This is a long period in the development of a human during which multiple changes in absorption, metabolic activities, physiologic and endocrine functions and other characteristics (as well as a changing exposure scenario) are known to occur. Although children and adults may respond with the same "mode of action" when exposed to an agent, it is also possible that they would not; for example, an enzyme which is essential to metabolize an agent may not even exist at some point in childhood. Specific organs, such as the thymus, brain or components of the reproductive system may not respond during childhood in the same way as does the adult organ. There are examples in the pharmaceutical, environmental, and infectious disease literature to indicate that organ systems during development can respond differently than when they are fully developed. With the exception of DES and radiation, most of the human examplesdo not include a risk of cancer. However, the variation in the responses by age in children have been quite strong suggesting that the differences are important and may be large. Some of these examples may simply represent differences in the stage of organ development at the time of exposure, but in other examples they may represent adverse effects. It is also possible that these differences can render children less, rather than more, susceptible than adults, and it may be that selective cancer may only appear after exposure to carcinogens during development.

Since childhood includes the period from preconception through adolescence, the Agency needs to consider not only the changes in development during that time period, but the potential for different exposure scenarios. Given that metabolic activation/deactivation of the chemical and organ physiology and sensitivity would be part of the consideration of a mode of action, both fetal and maternal metabolism must be considered in determining exposures. The mother and the fetus must be examined during *in utero* and transmammilary exposure since they represent not only two individuals with differing stages in metabolic capacity for an agent but also two related, but also probably differing in significant respects, genomic humans. The variation in humans can be greater than that seen in animals in toxicologic experimentation, and the interindividual variation seen during development could be greater than that seen between adult humans or the adults of any species.

When an agent produces a carcinogenic effect in standard bioassays using adult laboratory animals by a non-threshold mode of action (linear dose-response), then the relevant considerations in comparing adult and childhood carcinogenic potential include a) whether the target tissue and key events are the same in the developing human compared to the adult; b) the appropriate dose to the target tissue of the child compared to the adult; c) the latency period for development of the cancer (which may be much shorter when the exposure occurs in childhood); d) the sequencing of sensitizing and subsequent potentiating events; and e) the possible increase or decrease in the actual risk from the exposure. An example of increased risk (two-three fold) is seen when assessing the risk from radiation on breast tissue when the irradiation takes place in very young children (typically those treated for thymus enlargement (Shore, 19XX)). In these cases, the relative risk of breast cancer is higher than expected based on adult estimates and the cases occur with shorter latencies than those which might be expected from adult data (Hancock *et al*., 1993) .although the cancers are the same. The sensitivity arises from the fact that at puberty the breast is rapidly developing and the increased cell division renders the tissue more sensitive to a genotoxic event. However, it should be reasonable to incorporate this increased sensitivity into an aggregate risk for the whole population when linear extrapolations is applied to genotoxic agents that induce breast cancer. Some Members found that the radiation and breast cancer example indicates that the approach proposed by the Agency lacks sufficient conservatism. Other Members disagree, and note that this position presumes that all genotoxic carcinogens act like radiation in terms of age dependence. They assert that EPA's risk estimates under the proposed Guidelines are not organ-specific and the appropriate “correction factor” would not be known (except possibly in the case of known human breast carcinogens).

Another characteristic of children which must be considered when evaluating the potential mode of action or genotoxicity of agents is that they can have concentrated, high dose rate exposures to carcinogens. For example, breast feeding infants can receive an 80-fold greater daily dose to dioxin than the maternal dose (Hoover *et al*., 1990), and bottle fed infants can receive virtually all their fluid exposure to tap water, resulting in many fold increase in exposure to tap water borne pollutants above the general population. Other aspects such as pica behavior and dermal exposure have been widely discussed.

Regarding examples of notable physiological differences, the immune function of children undergoes constant change during the first few weeks of life, and immunity itself may be affected by events such as a standard vaccine schedule throughout infancy and young childhood. Compromised immune systems are known to increase the risk of cancer for some carcinogens. (e.g., ciclosporin (IARC, 1990)). The effect of these factors should, ideally, be considered when examining a chemical's differential effects on children and adults. The Subcommittee intuits that neither EPA nor any other risk assessors/risk managers know how (at this time) to incorporate these putative interactions into risk assessments. Consequently, these comments (as are other, similar suggestions in our report which push (or get ahead of) the state-of-the-art) are offered as suggestions for future incorporation into the Risk Assessment Guidelines, not recommendations for changes to the current document. Other Subcommittee Members noted the considerable growing literature on the topic and found that in the absence of specific information on these and other issues related to inherent childhood susceptibility, a modification of the current default approach should be considered to address these issues. However, they do support the use of the most conservative approach to risk assessment. Therefore, these Members feel it might be useful for the Agency to perform both linear and MOE risk assessments, and chose the most protective (which will generally be the linear approach).

The proposed Cancer Guidelines have focused on risks by organ site with limited consideration of cell type or other factors which have been shown to be important in humans and animals (e.g., nitrosamines and nitrosoureas). There is clear evidence in humans and animals that cancers can differ by cell type and that risk is dependent on the age and/or type of exposure (Ron *et al*. 1995; Hall and Holm, 1998; Vesselinovitch, 1983; Bosch, 1977; Anisimov, 1988; Drew *et al*., 1983; Hard, 1979; Meranze, 1969; Noronha and Goodall, 1984; Peto *et al*., 1984; Reuber, 1975; Russo *et al*., 1979; Shirai *et al*., 1989). Nevertheless, it is not scientifically defensible to, in general, make inferences about cell-specific risks, when extrapolating from animals to humans. Without human data, we do not have the confidence to assume site concordance, let alone cell concordance. Human data would be needed at this level of specificity and it seldom is available in large enough numbers. It would be important, therefore, when the means are available, to consider cell type as part of the scenario when examining potential risks from different modes of action, especially in children.

The use of a mode of action scenario to determine the risks of cancer from childhood exposures should involve a consideration of reproductive and developmental factors including two generational effects in the evaluation. Some Members noted the need to extend the body of scientific information to improve our ability to evaluate multi generational carcinogenesis through the conduct of transplacental and multi generation bioassays and mechanistic studies on a selected series of chemicals. The simultaneous review of modes of action raised from these other toxicological studies of effects in fetuses and the young should provide answers to some of the questions which have been raised regarding the use of mode of action data to assess the risks of cancer in children. For example, if there is evidence of thyroid or other endocrine effects on fetuses and young animals and the cancer's mode of action is through a thyroid or other endocrine mechanism, the two sources of information must be used to determine the applicability of an adult "mode of action" framework to children. The Agency should spell out what factors they will review in order to determine whether the mode of action of a carcinogen as identified in adults is applicable in children.

The general approach of the Agency to the application of Cancer Guidelines to risks of cancer from exposure to potential carcinogens in childhood should probably differ from that which is implied in the proposed Guidelines. This approach seems to be that, given there is no other information to the contrary, the Agency will assume that children are like adults and, with the use of default options to account for uncertainties, these should result in sufficient safety for children. Some Members of the Subcommittee believe that EPA's approach should make the basic assumption that children differ from adults in a number of specific respects. The approach should provide for the specific examination of factors that could place children at higher risk. Thus, the Subcommittee suggests that the Agency develop a list of such factors that might result in quantitative differences in dosimetry or responses and search for the appropriate information in the basic biomedical literature as it would apply to the agent under consideration. It must also be pointed out, however, that identifying such factors does not automatically point the way to modifying the risk assessment.

Some Members of the Subcommittee agreed with EPA’s default assumption that the mode of action should not be considered operative in children and a linear dose-response relationship be used unless a biological cogent rationale is developed or agent specific data is available. Some of these same participants recommended that more specific criteria for a biological cogent rationale needs to be developed. Specifically, the Agency should attempt to identify each step in which qualitative or quantitative differences in dosimetry or responses might be expected between children and adults and search for the appropriate information in the basic biomedical literature. Once differences are identified, EPA should try to determine if the risks are going to increase or decrease in accordance with the age specific changes

Other Members found the EPA’s default assumption and policy inconsistent with the EPA’s general conclusion that the mode of action is similar between children and adults (xii,xiii). They argue that default policies should be consistent with what EPA generally believes to be the case most of the time. It is particularly inconsistent to apply a linear dose-response relationship for the general population including sensitive subpopulation (p. xi of the draft document) even after a significant body of evidence has been developed to demonstrate a non-linear mode of action. A more consistent policy decision would be to apply a margin of exposure approach when a non-linear mode of action has been established in adults. EPA could require additional uncertainty factor if there is data to suggest that children are more susceptible than adults. This approach would facilitate harmonization between cancer and non-cancer risk assessment and still provide EPA with the flexibility EPA needs to be conservatively protective.

3.3 Protective Factors in Margin of Exposure Analysis

When applying the framework for assessing mode of action data establishes that linearity is not the most reasonable working judgment and that there is sufficient evidence to support a non-linear mode of action, the Guidelines' default position provides the use of a margin of exposure approach.. EPA asked that, given the considerations that need to be addressed in the framework (including the applicability of the mode of action to children), if the SAB agrees with the view that a separate factor to protect children, in addition to the usual factor for human variability, is not necessary in the margin of exposure approach.

The Subcommittee was unable to reach a consensus on this question. The Subcommittee did agree, however, with the supposition that, even after adjusting for differences in exposure, the population threshold for children could be lower than for adults for some carcinogens acting through a non-linear mode of action. In some cases, exposure in various developmental stages might cause the same incidence of cancer at doses many times smaller than in adults (and, as seen with DES, the cancer seen in individuals exposed *in utero* may not even occur in adults exposed to the same dose as the mother Current tests in animal species, even if conducted with perinatal exposure, may have limited predictive power for assessing risks of exposure in the human preconception, *in-utero*, and neonatal periods. **(Reference to be provided)**

Even if the mode of action is the same in these periods and in adulthood, that does not guarantee that sensitivity (as measured by minimum effective dose) would be the same (Murdoch and Krewski, 1988; Ron *et al.* 1995; Hall and Holm, 1998; Moolgavkar *et al.*, 1999)). Children are different in the fact that their underlying gene expression patterns may be different from adults and these differences could be exacerbated by environmental factors. Such factors can have substantial effects on their responses to xenobiotics. In addition, exposures in children have a longer period of time to manifest themselves and to accumulate subsequent critical exposures to other xenobiotics to complete the process of carcinogenesis.

On the other hand, the extent to which any of these special susceptibilities would be true for a substantial fraction of all carcinogens is not known. For cancers that manifest in early childhood, environmental factors might be relatively unimportant except in those children who have other susceptibilities such as a genetic predisposition causing a high baseline risk. However, findings such as the unexpectedly large increase in cancers in thyroid induced cancers in children and young adults following the Chernobyl accident (Moolgavkar *et al*., 1999) suggests caution in this regard. The Agency is already proposing to average exposure only over the relevant childhood years for carcinogens assessed by the margin of exposure approach. Some Members noted that procedure is more protective than the usual assumption, cited in the Guidelines, that aggregate exposure over all of life is the best metric for risk, which implies that dose should be averaged over an entire lifetime before comparison with a criterion dose (e.g., the NOAEL). Other Members noted that these adjustments may not be sufficient to compensate for not taking into account timing of exposure and increased sensitivity explicitly, and in the end may still represent underestimates in risk.

The Subcommittee's Members had differing perceptions about how often increased sensitivity of children vs. adults occurs in the world of regulatable environmental carcinogens in comparison to cases of similar or lower sensitivity in children. Nor was there agreement about how EPA should manage this state of uncertainty. At any level of conservatism, some carcinogens will turn out more dangerous to children than expected and others less. The balance between the former ("false negatives") and the latter ("false positives") is ultimately a policy judgment involving the values placed on each outcome (including not only monetary costs but also the costs of competing risks for the false positives). Therefore, some Members felt that EPA need not routinely apply a separate factor to increase children's protection (i.e., answering "yes" to the question), while others felt that such a factor would be appropriate. There was consensus that if EPA were to use such a factor, it should be dependent on the state of the database and not necessarily a single default number. In general, the Subcommittee was supportive of EPA's intent to evaluate the acceptability of an MOE on a case-by-case basis, supported by a narrative. Some Members felt that in the absence of specific quantitative information, increased susceptibility *in utero* and early in life should be assumed, particularly in cases where the experimental evidence and human data do not cover those periods, and a default factor should be applied. Other Subcommittee Members disagreed with the application of fixed numerical factors, and suggest using explicit uncertainty analysis and increasing the uncertainty boundaries. However, the Guidelines are not very clear about how a risk manager would reach a conclusion on the acceptability of the calculated MOE for a specific carcinogen, and decisions could be seen as too dependent on the risk preferences of the decision maker.

Finally, the Subcommittee notes that the MOE approach will typically result in a less stringent risk decision than the linear default procedure but this might not always be the case. The former outcome depends on the acceptable MOE, while the latter outcome would depend on the risk criterion used (which can vary by at least 100-fold depending on characteristics of the population at risk and other factors). Some Members felt that acknowledgment of this possibility in the Guidelines would be important as well as useful.

3.4 The Use of Default Options to Convert An Adult Dose to A Children's Dose

The proposed Guidelines describe default approaches for converting adult doses into doses applicable to children. The Subcommittee was asked to determine if these default approaches were reasonable, in light of what is known about doses to children, the information that will typically be available to the risk assessor, and the Agency's policy of erring on the side of children's health when information is not available.

The default approach for converting an adult dose to a childhood dose should examine the relevant characteristics of children before simply converting the dose using a standard default option. Children differ from adults, and even differ during the childhood time span in physiologic factors such as inhalation rates, absorption rates, clearances, and metabolism to name but a few. A simple conversion will often not be sufficient when some of these changes may determine an all or nothing result. The Subcommittee encourages the Agency to broaden the framework age adjustment beyond that of a size adjustment for basal metabolic differences.

Adjustment of dose from body weight to surface area by using the $W^{-e3/4}$ scaling factor reflects an adjustment for basal metabolic rate and a variety of related physiological factors such as rate of respiration, heart rate, etc. Rates associated with these processes in children are generally much more rapid than adults when judged on a body weight basis. However, rates of xenobiotic metabolism are probably much more generally lower in children, dependent upon which enzymes are involved in the metabolism. The metabolic rate can be increased or decreased and change dramatically during childhood.. In situations where the parent compound is responsible for the toxicity, the application of the $W^{-e3/4}$ factor is an adjustment in the wrong direction if the chemical's clearance is primarily dependent upon metabolism. If a metabolite is responsible for the toxicity it would be a appropriately conservative adjustment, but for the wrong reason.

The Subcommittee suggests that the $W^{-e3/4}$ adjustment be made for physiological differences between species and for extrapolating these variables to children. Additional factors may be required if there are significant PK/PD differences. Additional factors should be considered, however, depending upon how metabolism of related chemicals relates to the toxic effects being evaluated. If data on related chemicals does not provide sufficient insight, application of an additional default factor should be considered. In particular, these factors should be applied if it is probable that metabolism is likely to be the key determinant of clearance of the chemical from the body. In general, chemicals with relatively short half-lives in adults would be of most concern (i.e. this would not be a problem with dioxins or PCBs, but it could be very important with chemicals like dichloroacetic acid) and in fact, with chemicals with long half lives, the rapid growth of the child may significantly decrease the concentration of the chemical.

No scientific reason is provided why EPA should develop methodologies to adjust for inhalation and dermal exposures and not for oral dose, especially when information on area under the curve comparisons between children and adults are readily available from the pharmaceutical industry.

EPA states that the “data supporting the ¾ power factor pertain to cross-species equivalence, a fundamentally different question from determining equivalence across different life states of a single species.” This scientific rationale should be more carefully laid out. The Agency should accomplish this by:

a) Dealing explicitly with the problem of setting the most appropriate scaling factor for oral doses, rather than simply not applying a factor at all.

b) Determining a set of scaling factors for oral doses or provide better guidance for how to make judgements on the data that might exist for a chemical under consideration based on the general principles provided above.

c) Carefully review the basis for interspecies scaling and the extent that it provides guidance on adjusting cancer doses for humans of different sizes and ages.

It must also be noted that there is a distinction between "general metabolism" of children -- which will be much more rapid -- and their metabolism of xenobiotic agents, as well as the issue of differential maturation and regulation of enzymes resulting in a different metabolic profile. It seems inappropriate to discuss these two variables separately. When one considers xenobiotic metabolism, we also must distinguish between those processes that activate a chemical to a toxic form, and those which clear the toxic metabolism. An excellent example is the metabolism of the antibiotic chloramphenicol. Human newborns were dosed at the same level as used in adults. This resulted in the death of many newborns since chloramphenicol is cleared by glucuronidation and the human newborn has markedly decreased glucuronidation capacity as compared to the adult. For many, if not most, of the enzymes that are responsible for the metabolism of xenobiotics, the fetus and newborn have decreased activity as compared to adults. These enzymes include cytochrome P450 families 1, 2, and 3A4, and glucuronidation. There are a few enzymes that are higher or equal in the fetus than the adult, including cytochrome P450 3a7 and sulfatase. In the child the enzymes tend to be similar to the adult, but there are still clear differences (cytochrome P450 1a2 and 3a4 are higher in the child than the adult). The effects of these modulations on xenobiotic susceptibility can be to decrease or increase the adverse effects. Some Subcommittee Members wish to note that clearance of the parent compound from the body is only part of the overall process -- a process which perhaps may be too complex to capture via a simple scaling process. Individual agents have to be considered individually, including their metabolic profile with their potential to cause harm, including cancer. If the agent is metabolized at all this profile will undoubtedly change during development.

3.5 Adjustment of Slope Factors to Reflect Data on Early-life Sensitivity

The Subcommittee was asked to comment on the Guidelines' approach to adjusting slope factors to accommodate lifetime and partial lifetime exposure scenarios and reflect data on early-life sensitivity.

In general, the Subcommittee found that the methods used to handle the specified adjustments were appropriate. However, the Members also felt that there was considerable room for improving clarity of the presentation in the Guidelines document. This is especially true for the examples provided in Appendix F – they were not well explained. Example 3 (in which exposure occurs only during the first 10 years, yet two separate slope factors are combined) was especially difficult to follow, primarily because the need for both factors is not explained. This could be clarified by explicitly showing the linkage in ages between the animals and the humans. There is also no explanation of what happens in weeks 6-14, for which no animal data are provided.

Several other areas warrant comments. First, we suggest that EPA compare the proposed method to one using a theoretical cancer model (such as the multistage model that explicitly accounts for age-specific differences in tumor incidence rates), and analyze the results. Also, we have concern about the formula in the middle of page F-4, describing how risks for multiple tumor types are combined. EPA needs to formally discuss the addition of risks for different tumor types in the text and include a general formula for combining risks. We also question the use of upper bounds in the accumulation of these risks; there are methods available that could sum risks at the mean estimate and properly account for the overall variance of the accumulated risks, and this should be explicitly described (Gaylor and Chen, 1996).

There are at least three contributions to age dependent carcinogenesis to consider. The first entails inherent differences in susceptibility at different ages, for example, due to tissue susceptibility (e.g., from cell division or differentiation) and pharmacokinetics. The second has to do with the timing of the exposure, independent of inherent age susceptibility, and the third with the sequencing of the exposure in question with other endogenous and exogenous agents or disease states that affect the cancer process. Understanding these factors will require additional studies. At present a comprehensive and systematic state of the art review of the experimental and epidemiological literature on age dependent carcinogenesis, are not available, and are clearly needed. The Agency should then evaluate mathematical modeling approaches to take into account age dependencies. Clearly this is a key area in developing risk analysis with regards to children and an area in which additional research is needed.

3.6 Responses to CHPAC Questions

3.6.1 Data Required to Establish the Mode of Action for an Agent

The initial question posed by the CHPAC asked EPA to comment on the specific data required to establish a particular mode of action for a specific chemical agent. This is a complex question, and is addressed extensively in the Guidelines document itself. The Agency's response to the question is limited in length and thus rather cursory. It is a generic response when it appears details are requested. It does not specifically address children's issues. A more appropriate response would have made extensive reference to the appropriate discussions in the Guidelines document.

The Agency did note that a significant body of information is required to show that a specific mode underlies the process. Some Members noted that the Agency should also strongly convey that a high threshold of evidence is required to move to a non-linear approach, and expand on how it intends to apply the modified Hill criteria in the Proposed Guidelines; other Members did not hold this view. The response would be improved if the Agency noted specific information that would be required (e.g., which provide a clear understanding of metabolism and active metabolites in humans and test animals, clear evidence that the chemical and metabolites are not genotoxic, and for receptor mediated chemicals, clear evidence by the modified Hill criteria that the dose response relationship is non-linear). The Subcommittee was divided on the amount of evidence the Agency should convey as required to establish a mode of action.

The draft response was silent on how the Agency would surface and address competing (or multiple) hypotheses on the mode of action. This is particularly important since, given the limited number of scientists and resources available to investigate the mechanism of any particular chemical, research may proceed along one line of inquiry to the exclusion of others. It is important for the Agency to explain how the important process of surfacing the range of plausible hypotheses and subjecting them to experimental challenge and critical review is addressed in the framework of the Proposed Guidelines.

Dose additivity and its importance in assessing low dose responses has been widely discussed (see, e.g., Portier *et al.*, 1993; Hoel, 1980; Crump *et al.*, 1976; Lutz, 1990; Peto, 1978; Krewski *et al.*, 1995) and is particularly important in evaluating the quantitative relevance of the mode of action findings. This issue is acknowledged as important by the Agency (RAFTP, 1999, page 5) and should be discussed by them in the response to this particular question. Mode of action findings directly correspond to decisions on whether to perform a low dose linear or non-linear analyses. In cases where a low-dose non-linear mode of action is found, it is important to evaluate where on the dose response curve different subgroups within the population may lie.

Some Members believe that EPA should emphasize the importance of performing a screening level analysis to obtain, within an order of magnitude, an understanding of the magnitude of the background exposures to exogenous and endogenous chemicals in order to assess whether or not a non-linear approach is appropriate for the particular case in hand. This can be particularly important in assessing exposures to infants. An example of a general approach to this issue is provided in the Agency's draft assessment of 2,3,7,8-tetrachlorodibenzo-p-dioxin ("dioxin") and other dioxin-like compounds (US EPA, 1997). Absent such analysis the appropriateness of a non-linear analysis can be questioned.

People are exposed to a myriad of chemicals through the environment, consumer products, and the diet, yet a risk assessment frequently attempts to characterize risk from a single chemical by a single exposure pathway. Risk will depend on the exposure to the chemical under study (as well as other chemicals from natural sources and anthropogenic contributions from sources other than the one under consideration) that may operate by the same mechanism. So for example, if one were assessing risk of consumption of 2,3,7,8 TCDD-contaminated fish, the baseline would include exposures to other dioxin congeners, as well as to other chemicals that interact with the Ah receptor, such as PCBs, PCDFs, or even PBBs, other dioxins and dibenzofurans. However, it should be recognized that only when you inject non-linear or threshold behavior into the dose-response can risk be attributed among different sources.

Figure 1 illustrates hypothetical dose response curves under conditions of high and low background exposure for a chemical with a threshold occurring at a non-zero dose. For the first curve shown, background exposures are high, and risk increases linearly with increased dose. For

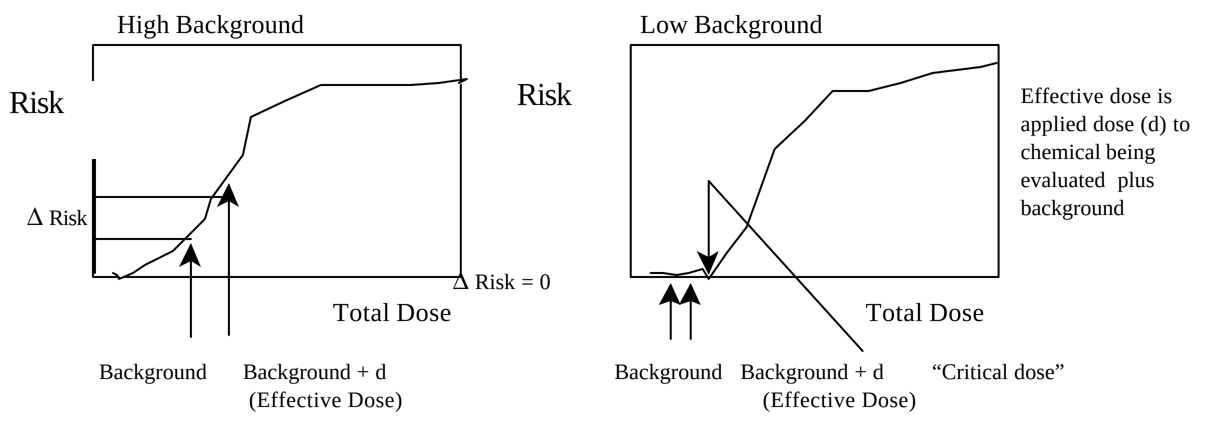

FIGURE 1

the second curve, background exposures are low and with incremental increase in dose "d", the exposure remains below the threshold, although the margin of safety is lower (total dose is closer to the critical dose or threshold). In the first case it would be more appropriate to assess risk using the linear procedure whereas in the second case the MOE approach would be appropriate.

Finally, in the response, the Agency should address how it plans to address the problem of site concordance. There are numerous examples of chemicals causing cancer at different sites in different species, and of substantial differences in the curvature of the dose response relationship for the same chemical at different sites (e.g., AAF, [Littlefield *et al*., 1979]; 1,3-butadiene, Melnick *et al.*, 1999}). A discussion is needed of the Agency perspective on this important issue, particularly as regards to modes of action findings resulting in low-dose non-linear analyses.

There is simply insufficient experience with the Guidelines to categorically state what data should be required or when it is sufficient to move away from the defaults. The most useful data would allow evaluation of dose response as well as mode of action. It is important to establish that a robust data set exists to determine that the mode of action affects cellular function in a non-linear fashion and that these responses are clearly coupled to the carcinogenic response before the conclusion can be made that a non-linear model is appropriate.

3.6.2 Modes of Action for Chemical Agents in Children and Adults

The CHPAC asked EPA to consider whether the modes of action for various chemical agents were different in children and adults. The Subcommittee's first concern with EPA's response is that this question cannot be addressed and answered in such a brief presentation as was attempted here.

The Subcommittee agrees with EPA, that, broadly speaking, the basic modes of action for carcinogens are likely to be similar in the developing human and adult. However, there can be major differences in the key steps that can contribute to the altered susceptibility of the developing human as compared to the adults' susceptibility to carcinogens and resultant cancer biology.

At one extreme, the similarities between modes of action in children and adults are easy to identify. There is no doubt that the principles of physical chemical and chemistry, molecular biology, etc. are the same in children and adults and that mutations and other basic processes involved in chemical induced cancer are similar. The critical question arises when one attempts to determine if the multiple molecular and biochemical processes occurring during development impact the basic processes underlying chemically induced cancers to such a degree that they impact on the mechanism(s) of action of an agent and the resultant biology of the cancer in the developing human as compared to the adult human.

The evidence to date suggests that, while the basic biological processes are the same in the developing human and the adult, the differences in development that impact the mechanism(s) of action are not identical in adults and the developing human and should be considered different. This is true for cancers that occur during childhood and cancers that occur in adults due to an exposure to a carcinogen during development. These examples will provide clear evidence that the above statement is true for at least two of the best studied cancer causing agents:

a) Diethylstilbestrol (DES) was administered to pregnant females to prevent miscarriages. The mother appeared to have no long lasting discernible effects while the offspring had birth defects of the reproductive tract and a very few female offspring developed clear cell vaginal carcinoma when they became adults. The fact that diethylstilbestrol was a human carcinogen only became known due to the rarity of the clear cell carcinoma. To date clear cell vaginal carcinomas do not appear at an increased rate in DES exposed mothers. However, as is the case for other estrogens, mothers are observed to have an increased risk of breast cancer (Giusti *et al*., 1995; IARC, 1979, 1987) and endometrial cancer (IARC, 1979, 1987). It is unclear whether these cancers will be seen in postmenopausal DES daughters. Thus, in humans, DES appears to cause only clear cell adenocarcinoma of the vagina and cervix in females exposed during development. Although the basic cancer causing processes may be found in both the adult and developing child, distinctly different cancers appear depending on whether the person is exposed during development or in adulthood. Interestingly, DES appears to increase the risk of testicular cancer in males exposed in utero, whereas in men treated with DES for prostatic cancer, there are some case reports of primary breast cancer (IARC, 1979 and 1987). Also, developmental changes in male and female reproductive organs were detected in experimental animals studies (Marselos and Tomatis, 19XX). It would be useful for the Agency to determine if experimental animal data would have led to risk assessments that would have prevented exposures in humans that lead to cancer.

b) Children show increased risk from radiation induced thyroid cancer when compared to similarly exposed adults, the magnitude of the effect of age at exposure on thyroid cancer is an area of ongoing research. (NAS/NRC, 1990) and the cancers generally occur with a shorter latency period (Ron *et al*. 1995; Hall and Holm, 1998; Moolgavkar *et al*. 1999). Observations on children exposed to radiation following the Chernobyl accident show a marked increase in their rates of thyroid cancer (Astakhova *et al.*, 1998). Unexpectedly early and large increases in the incidence of thyroid cancer have been reported in children and young adults following the Chernobyl accident (Cardis *et al*., 1996; Kazakov *et al*., 1992; Tronko *et al*. 1994; Tsyb *et al*., 1994; Bard et al., 1997). Further, thyroid cancer induced by low and brief external gamma radiation develop after exposures in childhood, but rarely after adult exposure (Ron *et al*., 1995; Hall and Holm, 1998). Although the NAS BEIR V committee estimated the risk from exposure during childhood to be about twice as large as the risk for adults, the committee noted "such estimates are still highly uncertain." A recent analysis of solid tumors of atomic bomb survivors by Kai *et al*. (1997), which contrasts NAS predictions with those developed under alternative models, suggests the effect of age on lifetime risk can have a considerably greater impact, and predictions on the magnitude of impact are highly dependent on model assumptions. Although the basic mechanism is mutation, the type of mutation can be different in the developing human as compared to the adult and the resultant biology of the cancer can be different. RET rearrangements of the PTC3 type were found but "all other genetic changes known from adult thyroid carcinomas, RAS and p53 in particular, appear to be irrelevant" in childhood thyroid carcinomas (**Need author,** 1988). Thus, although the overall mode may be mutation, the exact mutation and resultant thyroid cancers rates may be different in thyroid cancers of the developing human and adult exposed to radiation.

Incidence and type of cancers seem to be different in the developing human and the adult. Specific cancer type frequencies are different in children than adults. Childhood cancers tend to be of embryonal cell type, they have a different distribution of cancers than adult, and the percentage of tumor types change with age even during development (Christ, 1996). There are certain cancers such as Wilms tumor that are found primarily in children, and some cancers such as congenital or infantile neuroblastoma that can go into spontaneous regression, and the 4 year survival of children with neuroblastoma is much better in infants as compared to older children (Bowman *et al.*, 1991). Clearly cancer biology is different in tumors of childhood and tumors in adults. How environmental chemicals interact with the altered cancer biology during development and how the chemicals interacts with the familial and genetic linked disorders associated with malignancies of childhood such as chromosomal disorders, DNA fragility, immunodeficiency and their related childhood cancers is an area where additional studies are needed.

In summary, while the overall basic cancer causing modes of action and key steps of chemical induced cancers may be similar in adults and the developing human, the effects of development on the modes of action and key steps can be qualitatively and quantitatively different in terms of risk and not equal in the adult and developing human. These differences appear to be at least partially responsible for the altered susceptibility of the developing human to environmentally induced cancers. Therefore for clinical, practical and scientific purposes, while the modes of action of cancer in children and adults are similar for specific chemicals, they may differ enough, however, that they should be considered (overall) to be different for the purpose of risk assessment. The default decisions on how to address these potential quantitative differences are, however, clearly a matter of policy.

Finally, if a policy decision is made to base the risk assessment on the dose in the most sensitive age group associated with the key event (e.g. hormone levels, cell proliferation) in the fetus, infants, children and adults, as well as the elderly, many Subcommittee Members believe that the downstream steps leading to tumor formation at higher doses will be blocked for all age groups. Therefore, if there is general agreement that the mode of action is similar, preventing the precursor endpoint in the most sensitive age group will prevent the subsequent formation of tumors at higher doses. There are seldom data to adequately define sensitivity across different life stages, necessitating the need for policy in cases where data are lacking.

3.6.3 Data to Support Departing From A Linear Default Dose Response Assumption

The CHPAC tasked EPA to determine what constituted sufficient mode of action data to depart from a linear default dose response that is adequate for children and for adults. They also asked EPA's opinion as to what policy should be implemented in the absence of mode of action data to assure protection of children, and what policy should be followed if there are sufficient data to establish a mode of action in an adult, but not for a fetus or child.

EPA's answer to this question is too simplistic to address the concerns. The answer lacks any discussion as to how data generated in one subset of biological and physiologic processes (adult animals) can possibly be cogently and plausibly extrapolated to a quite different set of biological and physiologic processes (immature animals).

The case studies of agents T and Z in the appendices are particularly inadequate to address the concerns of extrapolating adult MOA data to immature animals. The postulated mode of action for chemical T was the continuous elevation of TSH levels that stimulates the thyroid gland, resulting in proliferation of the follicular cells leading to nodes then tumors. Key events associated with these mode included changes in liver T4-UDPGT **(will provide definition)**, an indicator of liver microsomal enzyme induction and enhanced liver metabolism. There are no data on carcinogenic outcome on immature animals, so it is not known if thyroid tumors are the only tumors caused as a result of this exposure (only adults were studied). One wonders if liver microsomal enzyme induction and enhanced liver metabolism occurred prenatally or in immature animals, are there other feedback loops which might be disrupted? What about aldosterone? Cortisol? Growth hormone? Somatomedin? Other hypothalamic-pituitary axis hormones? What other growth factors? This seems a very general phenomenon, and there are no data which show that other growth regulating systems are not affected. This is another area where considerable research needs to be undertaken before EPA can deal with such questions in assessing risk.

In the second paragraph of the case study, the discussion again focuses on thyroid cancer, and it is stated that the incidence of thyroid cancer in children is 1 per million following a prenatal or postnatal/early exposure; however, the development of cancer in the mature animal as a result of prenatal/childhood exposure is not addressed. The fourth paragraph states that the evidence supports the view that Chemical T's mode of action will not be different for children. Most Members of the Subcommittee disagreeand find that there is no evidence to support this finding. We believe, in fact, that there is biological plausibility that it may be different. Of course, unless one knows what the difference is, it is hard to take it into account in a quantitative risk assessment. Therefore one should use the most conservative approach until one has data specific for the developing organism. First, the carcinogenic potential of chemical T may not be limited to thyroid cancer. Second, the incidence of the tumors in childhood is not the only issue. It is also the incidence in both immature and the mature animals following prenatal/postnatal exposures.

For chemical Z, the mode of action in mature animals is postulated to be bladder tumor formation in male rats through a sequence of key events involving perturbations in urine physiology, especially increased urinary calcium concentration, calculus formation, urethral irritation, hyperplasia, and neoplasia. No data are available in immature animals. It would seem plausible that in a rapidly growing organism, increased calcium losses via altered urinary physiology would result in a number of systems being affected, including bone and altering various hormonal states such as parathyroid, calcitonin, and vitamin D. These effects may alter the cancer susceptibility of different organs (bone, parathyroid, etc.). These effects could be greater in the immature animal and may not be found in the mature animal. Indeed, in a recent article, end stage renal disease patients were found to be at increased risk of cancer, particularly of kidney, bladder, and thyroid and other endocrine organs (Maisonneuve *et al*., 1999). In addition, the highest risk was found in the youngest patients. The author of the case study assumes that altered urinary physiology is the only significant mode of action in immature animals. There is an inadequate basis for this assumption. There are many examples of chemicals whose major toxic effect in the mature animal is quite distinct from the major toxic effect in another developmental stage. Examples include lead (kidney in adults, brain in children), ethanol (intoxication in adults, malformation, intrauterine growth retardation including decreased CNS growth and permanent decreased neurologic function in the fetus). However, unlike the data available clinically, EPA will have cancer bioassays conducted at the maximum tolerated dose for 18-24 months that will identify many of the major toxic effects. EPA's comparisons of perinatal and adult carcinogenicity assays find the lack of complete site concordance is illustrated in numerous examples (e.g., vinyl chloride and hepatomas (Drew *et al.*, 19XX); ethylnitrosourea [Vesselinovitch *et al*., 1974); benzo(a)pyrene (Vesselinovitch *et al*., 1975a, b); diethylnitrosamine (Vesselinovitch *et al*., 1984) to name a few).

However, one Member of the Subcommittee believe that, lacking agent specific data on carcinogenic potential in immature animals (that means both cancers appearing in immature animals as well as cancers appearing in mature animals following exposure to immature animals), one cannot assume a specific mode of action and a linear default model should be used.

Most Members held a differing opinion, however, and the remainder of this section presents their viewpoint. They believe that a more appropriate default position is to assume that a mode of action for adults is generally relevant for children, *unless* there is evidence to suggest otherwise. A margin of exposure analysis should be used. An additional uncertainty factor could be incorporated if there are no agent specific data or cogent rationale supporting the comparability between responses in children and adults. This alternative proposal would take into account the substantial body of data that was generated to demonstrate that the mode of action supports non-linearity. As discussed earlier, there was majority position that the modes of actions are generally the same. The risk assessment process allows for the use of the incidence of a precursor effect to a tumor, such as a hyperplastic response, as the basis for its quantitative estimates of risk, not the incidence of frank tumors. The Agency usually includes an uncertainty factor of 10 to address susceptible populations. It is also public health-protective by allowing the Agency flexibility to add additional uncertainty factors to account for possible differences between children and adults in addition to those factors already required. This will allow for a more consistent approach with non-cancer endpoints that is appropriate for carcinogens for which there is persuasive evidence that the mode of action is nonlinear and/or secondary to other toxicities. This alternative default position is supported by the Agency's general conclusions that the mode of action for many agents are the same for children and adults (P. xii), that metazoans appear to share the basic modes of carcinogenic action (p.2-34), that evaluation of 40 rodent carcinogenicity studies with combined perinatal and adult chronic chemical exposure and adult chronic exposure alone resulted in similar types of tumors (pg..xiii), and that most often differences between carcinogenic effects can be traced to differences in metabolism and toxicokinetics.

3.6.4 Cancers Unique to Childhood or Resulting Later from Childhood Exposures

The CHPAC asked EPA to comment to on the extent to which it considered application of the Guidelines to cancers occurring uniquely in childhood, or to cancers that occur later in adolescent or adult life resulting from childhood exposures.

The Agency's response noted that it examined the pertinent literature as background to the development of the Guidelines. The main Guidelines document provide descriptions of the comparative data on early life and traditional bioassay that was developed in the review by McConnell (19XX). The data indicate that the main documented differences appeared with genotoxic agents administered during critical stages of development. There are animal data that support the issues raised about these agents that seem to parallel human experience. The Agency clearly stated in the main document that it would consider the dose-rate implications of shorter term exposures in these critical periods, so we do not see any particular problems here.

The major question, however, is not whether or how to deal with the genotoxic agents, but whether there should be some special handling of compounds that modify the endocrine, paracrine or autocrine factors that play very important parts in development. Although such effects in this area are not generally dealt with by a linear model, one has to ask at what point in a relatively short-term exposure can irreversible effects be produced? The mode of action may be similar to that in the adult, and if a non-linear extrapolation can be justified it should be carried over to considerations *in utero*, in the neonatal and adolescent periods. The dose-rate issues may also be identical, at least if measured at a tissue or cellular levels. Conversely, a short term change in a developmentally important endocrine, paracrine or autocrine factor could result in irreversible changes in the functioning adult which may lead to increased cancer risk. The question of additivity to background levels of the hormones and signalling agents could play an important role in this context. However, it is unclear how homoeostatic processes may reduce risk due to background levels of the hormones.

Ultimately, the question is whether something less than a lifetime exposure gives rise to an irreversible event, and we did not find this particular concern well articulated in the EPA response, although it does seem to be embedded in the approach as outlined in the Guidelines.

3.6.5 Latent Risks From Exposures at Different Developmental Stages

The CHPAC asked EPA to identify the factors that should be reviewed to determine the latent risks from exposures at different stages of development: pre-conception, in utero, in childhood, and in adolescence.

EPA's rather brief response does not answer adequately the question. The Agency guidelines addressed this issue at length and presented a large amount of animal data to show that there is not much difference in latency (EPA Draft Cancer Guidelines, p.2-15). It could not be determined whether the slight decreases in age of first tumor sometimes noted in the perinatal studies were due to the fact that dosing started earlier in these perinatal studies. The EPA might consider calculating risk estimates for the adult and perinatal carcinogenicity studies and compare potency estimates. Our interpretation of the question is that it calls for the identification of which specific *clinical* factors should be used to determine the latent risk from exposures at different developmental ages. These factors should include but should not be limited to:

a) an unusual age for presentation of the cancer
b) a rare cancer regardless of the age
c) multiple primary tumors
d) bilateral tumors at an unexpected age
e) excessive risk of cancer for an age group when compared to patients with similar exposures but who are older.
f) all the cellular and biochemical changes that may occur during development that may cause a higher degree of susceptibility at different stages of development

There are several studies and observations which ought to be brought into the response to this question. One of the best examples of the different effects of known carcinogen exposure at different ages is that of irradiation. Exposure to radiation in utero, infancy, and pre-adolescent period has a different effect on each period of development. Hancock *et al*. (1993) demonstrated that age at irradiation strongly influenced risk of breast cancer in women who received radiation therapy for treatment for Hodgkin disease. The relative risk (RR) of breast cancer was 136 for women treated before 15 years of age (95% confidence interval (CI) = 34-371). The RR declined as age at irradiation increased (Probability value (P) for trend < .0001), but the elevation remained statistically significant for subjects less than 30 years old at the time of irradiation (for those 15-24, RR = 19 [95% CI = 10.3-32]; for those 24-29, RR = 7 [95% CI = 3.2-14.4]). In women above 30 years of age, the risk was not elevated (RR = 0.7; 95% CI = 0.2-1.8).[4] The addition of mechlorethamine, vincristine, procarbazine, and prednisone chemotherapy to irradiation increased the risk within the first 15 years

Another example of the differential effects of a carcinogen at different stages of development is the well recognized exposure to DES (as noted above) and the differential effects between not only age of exposure but also sex. DES has been associated with an increased risk of breast cancer in mothers who took the medication. In contrast, longitudinal studies of daughters exposed *in utero* showed that they developed cervicovaginal clear cell adenocarcinoma. The study of DES daughters highlights the importance of longitudinal studies to identify carcinogenic risks, which were not observed in their mothers. Without such studies, and given the fact that vaginal clear cell carcinoma is such an extremely rare cancer, the full carcinogenic potential of DES on future generations would not be known.

Thus, there are examples that illustrate exposures to carcinogens at different development stages can influence the risk of cancer in humans.

3.6.6 Effects Related to the Timing of Exposure

The sixth question posed by the CHPAC asked for a description of how the proposed cancer guidelines take into account the timing of exposure, especially the effects of acute exposures during particularly sensitive developmental stages.[5]

The Agency answers this question for two different types of carcinogens – those that act by a mutagenic mode of action, and those that qualify for its threshold (“non-linear”) dose response procedure. For agents with a mutagenic mode of action, the Agency indicates it will employ estimates of daily dose averaged over lifetime and linear extrapolation, and that this will result in conservative estimates. Thus the Agency justifies not formally addressing age at exposure because it performs what

[4]These relative risk ratios apply to a relatively short period after exposure, during which the baseline rate for breast cancer is low in the females exposed at the younger ages. Estimates of absolute lifetime risk vary much less with age at exposure than might be inferred from these relative risks ratios. BEIR V (NRC 1990) suggests that breast cancer risk might be about 3 times higher for exposure at age 15 than for exposure at age 25. (See Figure 5.11 on page 260.) Note that BEIR V concludes that radiation at puberty carries the greatest risk. Radiation of prepubertal females doesn't appear to confer as much risk.

[5]As originally posed, this question also asked if new models based on acute or combinations of acute and chronic exposures were needed. The EPA, for purposes of clearer exposition, divided this question into two parts; the second of which addressed the modeling issue. This question is covered in section 3.6.8 of this report.

it considers to be a conservative dose response analysis. This is not an entirely satisfactory answer. However, elsewhere in the same document, the Agency states that "As consideration is given to children and other special populations that are defined by stage in life, it is clear that averaging doses over a full lifetime is not appropriate in all situations" (US EPA RAFTP, 1999, page 5). This statement, and the reasoning behind it, should be incorporated into the response to this question, and the justification for not addressing this important feature of childhood risk assessment rethought. In doing so, some of the key empirical and theoretical literature on the topic should be referenced.

The response indicates that for chemicals with a nonlinear cancer dose response relationship, sustained exposure at some critical concentration is needed, with the assumption being "...cessation of exposure, especially when it occurs early in the process, may result in a reversal of effects and the failure of tumor development." The issue of magnitude and exposure cessation needs to be assessed in the context of cumulative exposure to endogenous and exogenous agents operating by the same mechanism. The response should address how cumulative exposures are taken into account in assessing the timing and dose rate of chemicals assumed to operate via non-linear modes of action. Cumulative *simultaneous* exposure to the same organ or system determines whether the critical concentration is achieved and the location on the effective-dose response curve, and cumulative *sequential* exposure determines whether the required sustained exposure has occurred. The idea that early cessation of exposure to non-linear chemicals results in reversals should be discussed in terms of the available evidence from data on early in life exposure experiments and epidemiology (e.g., *in utero* and early in life saccharin data (e.g., Taylor *et al*., 1980) and modeling (Cohen and Ellwein, 19xx); diethylstilbestrol induced cell-cell adenocarcinoma of the cervix and vagina (IARC, 1987; Giusti *et al.*, 1995), and modeling exercises (e.g., Murdoch and Krewski, 1988).

Factors important to assessing age-dependent carcinogenesis were discussed in section 3.5, along with a recommendation for research on these issues. Such research is also suggested to buttress EPA's response to this question. There are a number of experimental reports, some of which show large differences in susceptibility with age, in single or and multi-dose studies (see e.g., Peto *et al*., 1984; Vesselinovitch, 1983; Bosch, 1977; Anisimov, 1988; Drew *et al.*, 1983; Hard, 1979; Meranze, 1969; Noronha and Goodall, 1984; Peto *et al.*, 1984; Reuber, 1975; Russo *et al*., 1979; Shirai *et al*., 1989), and others which show no differences (McConnell, 1992). In some cases, age susceptibility data were mostly explained by pharmacokinetics and by increased cell turnover (e.g., vinyl chloride [Laib *et al*., 1989; Swenberg *et al*., 1992]), other cases by differentiation (e.g., 7,12-

dimethylbenz[a]anthracene (Russo *et al.*, 1979), and still others by age at exposure (e.g., radiation and solid tumors [Kai *et al.*, 1997]).

3.6.7 Assessing Risks to Special Populations

The CHPAC expressed concern about the application of the Guidelines in various types of exposure assessments, and, in particular, in dealing with regulations such as the Worker Protection Standard where consideration needs to be given to the actual exposure of children in farm worker families. They asked if the Guidelines set forth examples of such applications.

The EPA's Risk Assessment Forum Technical Panel (RAFTP) answers this question with the simple statement that the Agency's exposure assessment guidelines require that separate analysis be conducted for definable subpopulations believed to be highly exposed or susceptible. The answer also refers to "generic issue 3," in which the RAFTP refers to the information provided in EPA's Guidelines for Exposure Assessment and Exposure Factors Handbook, which both discuss how exposure might vary with age. The Subcommittee understands that EPA intends to deal with such issues on a case-by-case basis, for example by doing a separate exposure and risk assessment for farm children when assessing pesticide use. Although the examples in Appendix F of the draft Guidelines concern an inhaled carcinogen for which exposure (in terms of air concentration) does not differ between children and adults, that example could be extended to show how different exposure as well as different susceptibility can be included in risk assessments for children. The Subcommittee believes that the Guidelines would be strengthened by further examples, e.g., a pesticide example.

One of the sub-issues in this question, regarding how exposure assessments would be applied in developing regulatory policy regulations such as the Worker Protection Standard, does not appear to have been directly answered. Because we were unsure about what specific concerns of the CHPAC prompted this sub-question, we did not arrive at a conclusion as to whether this omission was important. The Subcommittee believes that the Agency's response was perhaps overly brief and superficially non-responsive, but not inappropriate. We suggest that the discussion in Appendix F should be strengthened. If EPA decides not to add an example specifically directed to children's exposures, it should consider whether it could also add a few sentences to Appendix F on how the assessment could incorporate differential exposure as well as differential susceptibility.

3.6.8 New Models for Acute or Combinations of Acute and Chronic Exposures

As part of their sixth question (see section 3.6.6 of this report), the CHPAC also asked if new exposure models for risk assessment were needed. The EPA's response to this portion of the question suggests that the assumption that risk is proportional to average dose is inconsistent with current toxicological concepts, especially when duration, frequency, timing, and magnitude of exposure vary considerably. The response indicates the difficulty of formally and fully taking into account dosing regimens in risk assessment and that techniques for doing so are not ready for general use. However, there are examples applying age dependent models which produce more satisfactory results than analyses based on lifetime average dose (e.g., Kai *et al*., 1997; Moolgavkar *et al*., 1993). These examples should be reviewed and considered. As a side issue, one of the impediments to improving the state of the art in modeling age dependence and having it recognized and accepted is the complicated mathematics involved in the analysis. Although the Agency has excellent staff with competence in this area, we understand that they are few in number. Some attention should be given to resources in attempts to improve the state of the art.

3.6.9 Research to Evaluate Unique Susceptibility of Children and High-risk Populations

This question from the CHPAC asked EPA to identify research it ought to sponsor in order to improve its ability to evaluate uniquely the susceptibility of high-risk populations, including children, to cancer.

When EPA develops its final response to this query, it should perhaps point out that this question is somewhat "loaded" in that it implies that children are, *prima facie*, more susceptible than other populations. There are differences between children and adults that can make them more or less susceptible. The presumption that they are uniformly more susceptible is not supported by current knowledge. The EPA's response to this question needs to be placed into the context of overall risks to children and other *potentially* high risk populations. Cancer risk may not be the most significant problem for children. One recently published study concluded that the incidence of childhood cancers was not increasing (Linet *et al*., 1999). Some Members felt that the lower incidence of cancer in childhood does not take into account the cancers that appear in adults that are at least partially due to exposure of the individual to carcinogens during childhood. However, there is no data to support the view that adult cancers are increasing. In fact, the data reported by Wingo *et al.*, 1999 indicates that there is no peak increase in cancer incidence at any age range that would suggest that exposures to children are leading to increases in cancer later in life.

The importance of quantitatively analyzing the available experimental and epidemiological literature on age dependence in carcinogenesis, in a comprehensive and systematic review, would be very helpful. This would provide a better foundation for decision making, as well as help in the design of future experimental and modeling research. The EPA's qualitative review of rodent carcinogenicity studies with a perinatal exposure component was based on the qualitative review of McConnell's (1992) which was undertaken "to examine the question whether the standard bioassay approach is or is not 'missing' potential chemical carcinogens" (McConnell, 1992, p. 67). The Agency added 13 chemicals, with all but one found by the Food and Drug Administration to be inactive in chronic studies, and three chemicals studied by the National Toxicology Program. The review was based on chronic studies with combined perinatal and adult exposures, and did not include the large body of data that did not meet the inclusion criteria (see e.g., Calabrese and Blain, 1999; Peto *et al*., 1978; etc.) and did not rigorously evaluate dose response relationships. In terms of dose response issues, the review was also limited by the high incidence in some of the studies and the innocuous nature of some of the chemicals studied. A comprehensive approach is clearly needed, with further in depth review of substances for which inherent early in life susceptibility is identified.

It would be useful for the EPA, in its response, to encourage or commit to the development of data in the chronic bioassay to contribute to knowledge on this issue. Meanwhile, however, rather than wait the 10 or more years for the development of the data, the Agency should quantitatively review the existing data and apply more realistic approaches to the analysis of risks from age varying exposures. One suggestion is to calculate risk estimates for the adult and perinatal carcinogenicity studies and compare potency estimates. The existing bioassay could be expanded to include the addition of dose groups with early in life exposure followed by stopping exposure, and sacrifice at the end of the study. Once a number of data sets have been analyzed and quantitated the issue can be revisited. In the interim, an intermediate approach to the problem is needed, for example to account for timing of exposure the inclusion of an extra default factor or a weighting function for age varying exposures based on models of multistage carcinogenesis with clonal expansion (e.g., Moolgavkar and Luebeck, 1990; Murdoch and Krewski, 1988). Additional adjustments to account for pharmacokinetics and increased tissue susceptibility at early ages for certain types of chemicals and tissues should be considered as well. The adoption of an interim approach would likely also encourage considerable research.

With the above in mind, it is useful to consider several areas of specific research recommendations. An important issue is that of addressing dosimetry issues more explicitly and adequately. Approaches to dosimetry must somehow take into account all the changes in response that occur in development, from preconception to adolescence. These should take into account those changes in physiology and biochemistry that mediate the response of the fetus, the nursing child, the toddler, and later developmental stages, to exposure. Some of this can be taken into account by understanding the nature and expression of enzymes responsible for metabolic clearance that activate and deactivate given compounds. These need to be incorporated into toxicokinetic models that consider the dosimetry of the responsible agent to the target site of concern. Clearly, this requires some basic knowledge of how the chemical is handled by various type I and Type II enzymes such as the cytochrome P450 dependent family of enzymes or glutathioine transferases that are expressed differentially during development. However, we also must acknowledge that we do not know how to do this now and that it will take a concerted research program just to establish the backdrop of general information into which chemical-specific knowledge of metabolism can be inserted.

An interesting process that plays an important role in development that could be of particular importance in understanding the true sensitivity of the young to cancer are effects on apoptosis. Suppressed apoptosis probably plays a role in the induction of cancer by some chemicals. To the extent such cells retain replicative potential, suppression of apoptosis could give rise to increased risk to cancer in the young. This may not be linear at low doses, but at effective doses, it could be a substantial enhancer of responses at doses where the compound is active.

The above specific areas notwithstanding, the Subcommittee sees the need for a large (hopefully coordinated across the government and the private sector), ongoing effort to document the many differences in physiological/biochemical/metabolic processes between children and adults, and understand how these differences impact human health and disease process. This task is complicated further by the fact that the population “children” is actually several (currently) ill-defined sub-populations at differing developmental ages, with differing responses to insult in the areas noted above (since all the different molecular & cellular processes do not mature at the same time or rate during human development or mammalian development). Until this effort is realized, risk assessment will be forced to rely on various assumptions and approximations, which may or may not be public health protective.

3.6.10 Accounting for Sequencing/Sensitizing/Potentiating Events

The CHPAC asked EPA to explain how the proposed GL address the sequencing of sensitizing and subsequent potentiating events in the manifestation of cancers both in childhood and in later adolescent or adult life.

The Agency's response to this question is somewhat indirect, and focuses on scientific uncertainties that exist and that may be reduced by future research, rather than on the defaults in the current Guidelines intended for use when uncertainties exist, or on the provisions of flexibility to depart from these defaults as scientific understanding advances and data are available in specific cases. Statements such as, "The Agency believes that in the future it will be through mechanistic studies…that will allow the guidelines to be applied to this question," imply that the current version of the Guidelines just ignore the absence of data, and cannot be applied, which is not the case. A more satisfactory response would be to indicate that, while guidance on this issue is not provided, the Agency is committed to carefully evaluate the empirical and theoretical literature and consider possible adjustments in its procedures to address it. This response should describe the conservative defaults (e.g., linear procedures and incorporation of a margin of exposure) that add a level of protection for susceptible populations for which empirical risk data may be absent.

The last sentence in the EPA's draft response ("To the extent that such information is available as to the staging of carcinogenic events, it should be incorporated into risk assessments") is moving in the right direction, but "should" might be changed to "can." The example in the Guidelines showing how analyses might be conducted separately by age group is an example of how heterogeneous risks can be incorporated into quantitative estimation procedures, when such data are available. The response to the CHPAC's question might describe this approach, and it therefore would be a useful exercise for the Agency to develop some example risk assessments which take it into account. It would be helpful for the Agency to outline how, for certain classes of agents (e.g., potent mutagens) and tissues (e.g., breast), the Agency believes risk is affected by sequencing, and the degree that it believes risk might be mis-estimated by not taking it into account.

4. CONCLUSIONS

Although the Subcommittee concluded that the draft guidelines might not be protective for childhood exposure to some carcinogens under some circumstances, it was not able to reach consensus on how frequently such instances might arise or on what steps EPA should undertake to address that possibility. The Subcommittee recommends that EPA issue the Guidelines promptly, with attention to the suggestions in this report, and then undertake a program of research and risk assessment improvement that will enable it to address the childhood susceptibility issue more completely in a future revision of the guidelines.

The following discussion summarizes the Subcommittee's findings (often expressed as a range of views rather than a consensus) on the five initial issues posed by the Charge.[6]

Issue a(1) addressed the use of a linear default approach and the degree to which use of this default position represents an appropriate public health protective approach for children. There was a division of opinion within the Subcommittee on this issue. Most of the Subcommittee agreed that the linear default approach (using the "upper bound" estimate) was sufficiently conservative. Other Subcommittee Members disagreed with the Agency's position, and hold that the degree to which the current procedure used for estimating risk at low doses mis-predicts risk is a matter of speculation, so there is no assurance of public health protection.

A related issue (a(2)) addressed the Mode of Action (MOA) Framework's requirement for provision of a scientific rationale covering the possible similarities and differences of the MOA among the human population, which judgment could be made from inferences without actual data on the various subpopulations. The Subcommittee believes that the Mode of Action Framework for analysis of data, as posed by the Agency, should be relevant for most subpopulations of concern. However, in the case of children, it would be important to consider a special evaluation which would determine whether all assumptions based on an adult "mode of action" would apply across the entire time-span of

[6] The Committee also evaluated the responsiveness of the draft guidelines to the questions posed by the EPA Children's Health Protection Advisory Committee in its May 12, 1999 letter to Administrator Browner. Although the Committee judged the responses for the most part to be adequate, some were rather perfunctory and incomplete. Several suggestions for improvement are detailed in Section 3.6.

childhood.. Since childhood includes a long period from preconception through adolescence, the Agency needs to consider not only the changes in development during that time, but the potential for different exposure scenarios.

Charge issue (b) asked for the Subcommittee's thoughts on the default use of a 10-fold adjustment factor (when application of the Framework for assessing mode of action data establishes that linearity is not the most reasonable working judgment and that there is sufficient evidence to support a nonlinear mode of action) to account for the variability in cancer responsiveness in the general population, unless case-specific information indicates that a greater factor is appropriate. The Subcommittee was unable to reach a consensus on this question, but did agree with the supposition that, even after adjusting for differences in exposure, the population response threshold for children could be lower than for adults for some carcinogens acting through a non-linear mode of action. On the other hand, the extent to which any of these special susceptibilities would hold for a substantial fraction of all carcinogens is not known. Various Members had differing perceptions about how often increased sensitivity of children actually occurs. Some Members felt that EPA need not routinely apply a separate factor to increase children's protection, while other Members felt a separate factor should be applied unless it was proven not to be relevant. There was consensus that if EPA were to use such a factor, it should be dependent on the state of the database and not a single default number. In general, the Subcommittee was supportive of EPA's intent to evaluate the acceptability of an MOE on a case-by-case basis, supported by a narrative.

There was a difference in opinion on the general risk assessment approach that the Agency outlined (GL p.2-34) in addressing human relevance of mode of action to children. Some Members of the Subcommittee agreed with EPA's default assumption that the mode of action should not be considered operative in children and a linear dose-response relationship be used unless a biologically cogent rationale is developed or agent specific data is available. Other Members found the EPA's default assumption and policy inconsistent with the EPA's general conclusion that the mode of action is similar between children and adults (GL p. xii-xiii). A more consistent policy decision would be to apply a margin of exposure approach when a non-linear mode of action has been established in adults. EPA could require an additional uncertainty factor if there are data to suggest that children are greater than 10 times more susceptible than adults. This approach would facilitate harmonization between cancer and non-cancer risk assessment and still provide EPA with the flexibility needed to be conservatively protective.

The Subcommittee was asked in Charge element (c) to comment on the default approaches for converting adult doses into doses applicable to children. The Subcommittee felt that the Agency must assure that the defaults take into account, within the capability of the extant knowledge base, all the changing biological factors of childhood development. Thus the Subcommittee encourages the Agency to broaden the framework for the age adjustment of dose beyond that of a size adjustment for basal metabolic differences. However, if the Agency continues under the current framework, it should be internally consistent in its approach to adjusting doses for the various routes of exposure. More specifically, the Subcommittee noted that EPA's default approach for converting an equivalent dose for adults to an equivalent dose for children is unclear and needs better definition. .

Charge element (d) asked if the approach to adjusting slope factors for lifetime and partial lifetime exposure scenarios to reflect data on early-life sensitivity is appropriate. In general, the Subcommittee found that the approaches were appropriate, but some Members felt the procedure might be improved. These Members encouraged the agency to evaluate mathematical modeling approaches to take into account age dependencies and to conduct as part of this evaluation a comprehensive review of the epidemiological and experimental literature on age dependent carcinogenesis. However, the Members also felt that there was considerable room for improving clarity of the presentation in the Guidelines document, especially in the examples provided in the Guidelines' Appendix F.

The Subcommittee recognizes the great care and effort that the EPA has applied in developing these draft Guidelines. The Subcommittee commends the EPA on their diligence. The EPA and the Subcommittee appreciates the need to have the Guidelines be health protective, particularly to children, and scientifically valid, while making sure the document is a living document that allows the applications of new knowledge, thought, and technology.

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